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授与した学位	博　士
専攻分野の名称	工　学
学位授与番号	博甲第４９８６号
学位授与の日付	平成２６年　３月２５日
学位授与の要件	自然科学研究科　化学生命工学専攻 （学位規則第５条第１項該当）
学位論文の題目	Studies on Synthesis of Novel *N*-Heterocycles and Their Antimalarial and Anticancer Evaluations （新規 *N*-ヘテロ環の合成と抗マラリアおよび抗ガン活性評価に関する研究）
論文審査委員	准教授　井口　　勉　　教授　菅　　誠治　　教授　大槻　高史

学位論文内容の要旨

The risk of cancer and malaria infectious diseases is increasing worldwide. Exploring new drugs to meet the needs against drug-resistant diseases is an everlasting demand the therapeutic practice. Meanwhile, the importance of microwave synthetic method is well acquired as the energy-saving tool. Plants are still an important resources for the discovery of new drugs. The author described the synthesis of novel *N*-heterocycles and their application to biologically relevant compounds and azo-dye material, which is comprised of three topics as described below.

(1) Microwave-Irradiated Synthesis of 1,2-Dihydropyridines from *N*-Functionalized Enaminones and Enals through Domino Condensation and 6π-Azaelectrocyclization

The The author examined to construct *N*-amino-substituted 1,2-dihydropyridine motifs using cyclohexane-1,3-diones via the Knoevenagel condensation with enals followed by 6π-electrocyclization using ethylenediammonium diacetate as a catalyst under MW irradiation. A survey of substituents on the N atom of **1** indicated that the phenylamino and benzoylamino groups are favorable for formation of 1,2-dihydropyridines, while phenyl, benzyl, and no-substituent are not. The substituent R^1 at C2 of enals **2** is crucial for smooth formation of the corresponding adducts and slightly higher yields are obtained with enals bearing an electron-withdrawing aromatic ring at C3. The synthesized 1,2-dihydropyridines **3** and **4** were tested against the human leukemia MV4-11 cell line. IC_{50} values are in the range of 2.2~5.5 μM with the compounds **3** series, which are comparable with the anticancer drug cisplatin, while no cytotoxicity was found with the compounds **4**.

(2) Synthesis and Antimalarial Activity of Neocryptolepine Analogues Carrying a Multifunctional Linear and Branched Carbon-Side Chains

The author prepared a novel series of neocryptolepine derivatives by systematically varying the nature and length of the substituent's on the neocryptolepine core. All the synthesized compounds showed potent antiplasmodial activities against CQS (NF54) *in vitro* over the neocryptolepine. The most potent and selective compound of these derivatives, **14,** showed antimalarial activity with an IC_{50} of 2.2 nM and a selectivity index of 1400. The compound **15** showed the highest β-haematin inhibition with IC_{50} value of 10.07 μM among the tested compounds. While, the compound **15** with branch side-chain has low cytotoxicity with IC_{50} of 7249.3 nM.

(3) Synthesis, in Vitro Antiproliferative Activity and SAR Study of *11*-Aminoalkyl Neocryptolepines Carrying Branched Carbon-Side Chains

A set of neocryptolepine analogues having diversified side-chain by varying the nature and length of the linker between the two nitrogen atoms as well as the substitution pattern and basicity of the distal amino group were examined. Many of these neocryptolepine derivatives **13a n** analogues have submacromolar antiproliferative activity against human leukemia MV4-11 cell line. Among them,1-amino-3-((2-chloro-5-methyl-5*H*-indolo[2,3-*b*]quinolin-11-yl) amino)propan-2-ol 1**3e** was the most cytotoxic with a mean IC_{50} value of 0.015 μM against human leukemia MV4-11 cell line.

論文審査結果の要旨

The risk of cancer and malaria infectious diseases is increasing worldwide. Exploring new drugs to meet the needs against drug-resistant diseases is an everlasting demand in the theraptic paractice. Meanwhile, the importance of microwave synthetic method is well acquired as the energy-saving tool. In this thesis the author engaged with the synthesis of novel *N*-heterocycles and their application to biologically relevant compounds and azo-dye material, which is comprised of four topics as described below.

1) The author examined to construct *N*-amino-substituted 1,2-dihydropyridine motifs using cyclohexane-1,3-diones via the Knoevenagel condensation with enals followed by 6π-electrocyclization using ethylenediammonium diacetate as a catalyst under MW irradiation. A survey of substituents on the N atom indicated that the phenylamino and benzoylamino groups are favorable for the reaction. The substituent at C2 of enals is crucial for smooth formation of the corresponding adducts.
2) The author prepared a novel series of neocryptolepine derivatives by systematically varying the nature and length of the linker between the two nitrogen atoms on the neocryptolepine core. All the synthesized compounds showed potent antiplasmodial activities against CQS (NF54) *in vitro* over the neocryptolepine. The data also demonstrated that a branched structural motif is not superior for antimalarial activity over a linear side chain, but their thioureido derivatives showed lower cytotoxicity than the linear one. Ureido and thioureido derivatives also showed stronger β-haematin inhibition than the corresponding free amines.
3) The author described the synthesis and antiproliferative evaluation of several neocryptolepine analogues carrying branched dibasic side chain at C11. A set of neocryptolepine analogues having diversified side-chain by varying the nature and length of the linker between the two nitrogen atoms as well as the substitution pattern and basicity of the distal amino group were examined. Many of the prepared neocryptolepine derivatives showed antiproliferative activity of less than μM against the human leukemia MV4-11 cell line. Some 11-(3-amino-2-hydroxy)propylamino derivatives showed the cytotoxicity with a mean IC_{50} value of 0.042 μM /0.057μM against MV4-11 cell line, 0.197/0.1988 μM against A549 cell line, and 0.138/0.117 μM against BALB/3T3 cell line.
4) The author prepared the neocryptolepines bearing azo-dye chromophore and their absorption spectra were discussed for further application as the pigment of textiles.

It can be seen from these results, the research indicated by this paper is worth as a doctoral dissertation (Dr., engineering).